REMARKS/ARGUMENTS

7 claims, claims 11 through 17, are pending in this application. It is believed that no new matter is introduced by the present amendments to the claims.

Claim Rejections – 35 USC §112, Second Paragraph

Claims 11-17 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Office has asserted that the claims are indefinite because they do not set forth the relationship between preventing platelet aggregation in a patient and inhibiting platelet aggregation in said patient. Claim 11 has been amended herewith to more particularly point out and distinctly claim the subject matter which applicant regards as the invention. The method is directed to inhibiting platelet aggregation in a patient. It is respectfully requested that this rejection be withdrawn in light of this amendment.

Claim Rejections – New Matter

Claims 11-17 have been rejected as failing to comply with the written description requirement, as containing new matter. The amendment of claim 11 provided herewith is fully supported by the subject matter in the specification: on page 6, at lines 21-23; and from page 7 at line 29 through page 9 at line 24. Also, it is established that a recitation in a claim need not be found verbatim in the specification, it must find support in the specification. *In re Anderson* (CCPA 1973) 471 F.2d 1237, 176 USPQ 331. Here, that support is found in the specification at the places here indicated. Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections – 35 USC §112, First Paragraph

Claims 11-17 have been rejected under 35 U.S.C. §112, first paragraph, as not being enabled by the disclosure. The material in the specification that is specifically delineated herein above provides clear support for the present invention providing a method for inhibiting platelet aggregation in vitro (acknowledged in the present Office Action on page 4, first paragraph), but it is asserted that the specification does not provide an enabling disclosure for a method of ***preventing*** [emphasis added] platelet aggregation in a patient

comprising administering to a patient in need thereof an effective amount of a ketolide. The claims have now been amended to more clearly indicate that the invention is concerned with inhibiting platelet aggregation in a patient in need of such platelet aggregation, with examples provided of specific conditions that may be ameliorated by such inhibition. The claims as currently amended **are** enabled for the reasons given below, and undue experimentation would not be required for a person of ordinary skill to practice the claimed invention.

The Wands factors to be considered in determining whether a disclosure would require undue experimentation include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." In re Wands, 858 F.2d 731,737; 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The Office has focused on the following factors in its rejection.

1) Nature of the Invention & Breadth of the Claims

The claims as amended are drawn to a method of inhibiting platelet aggregation in a patient in need thereof. The specification provides experimental data in the form of a table that compares ketolide activity against a standard compound known in the art, aspirin, in an *in vitro* platelet aggregation assay. The nature of the presently claimed invention is an extension of this demonstrated *in vitro* platelet aggregation inhibition to the similar inhibition in a patient in need of inhibition of platelet aggregation.

2) Relative Skill of those in the Art, State of the Prior Art, Amount of Direction or Guidance Presented & Presence or Absence of Working Examples

The Office has asserted that the ketolides of the invention are working according in this claimed invention according to a syllogism presented on page 6 in the current Office Action. Furthermore, the Office has asserted: "Accordingly, the specification's assertion of treating atherosclerosis is based solely on the anti-*Chlamydia pneumoniae* activity of the ketolides." These assertions are incorrect. The *in vitro* platelet aggregation assay data presented in the specification clearly show that the subject ketolides directly inhibit platelet aggregation. The assay did not involve the use of *Chlamydia pneumoniae* in carrying it out. Accordingly, the syllogism does not apply to the claimed invention. The subject ketolides have been found by the inventors to **directly inhibit platelet aggregation**. As indicated on page 6 of the specification at lines 21 –23, the inventors recognized that: "The ketolides

exhibit an anti-platelet-aggregating and antithrombotic activity, as shown by the results obtained in the experimental section disclosed below." The suggested treatment of arterial thrombotic complications associated with atherosclerosis with the subject ketolides was not based on activity against *Chlamydia pneumoniae* at all, and certainly not based "solely" on such an activity.

The skilled person for purposes of enablement here would be the director of drug development at a pharmaceutical company. Such a director would have a supporting staff of biologists, pharmacologists, toxicologists and formulation chemists. They would be capable of running additional *in vitro* assays (biologists); any required animal or human tests for drug absorption, distribution, metabolism and elimination (pharmacologists); any safety tests (toxicologists); and any formulation development needed (formulation chemists). Accordingly, the skilled person would be able to find practical dosage forms and dosage amounts for practical use of the claimed method, without undue experimentation. Such experimentation would be what is typically carried out in the pharmaceutical industry by such a skilled person.

The Office has cited the Kullo reference as indicating that "the use of antiplatelet aggregation tests are unpredictable and take long periods of time to fully develop adequate results." The decision in *In re Wands* cited above indicated that the test for what is "undue experimentation" "...is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (citing *In re Jackson*, 217 USPQ at 807). The present specification provides an assay for testing the ketolides of the invention and the Office has not demonstrated that the experimental studies lasting for several years would be "undue".

3) Quantity of Experimentation Necessary & the Unpredictability of the Art

As indicated above, the skilled person here would be capable of determining the proper dosing for carrying out the method now claimed. An assay for platelet inhibition has been provided in the specification, and the development of a dosing regimen and suitable formulation for carrying out the claimed method would be practical for the skilled person. The Office has cited the Hiatt reference as indicating that the efficacy of dipyridamole was difficult to demonstrate. However, the efficacy of clopidogrel (Plavix®) as an inhibitor of platelet aggregation has been shown clinically and that compound has been commercialized. The package insert for that compound is appended to this response. Clearly from the

successful development of this inhibitor of platelet aggregation, it can be seen that such a method can be carried out without undue experimentation. Thus, the Office has not met its burden of proof that undue experimentation would be necessary to carry out the presently claimed method. Withdrawal of the rejection is respectfully requested.

Claim Rejections – 35 USC §102

Claims 11-17 stand rejected under 35 U.S.C. §102(e) as being anticipated by Leadlay et al. (U.S. 6,437,151). The Leadlay reference teaches a method of treating infection by *Chlamydia pneumoniae*. This reference is not concerned at all with platelet aggregation. The Office has asserted that it is an inherent property of the ketolides of Leadlay to inhibit platelet aggregation. However, this reference does not provide any disclosure whatsoever concerning platelet aggregation. The treatment of an infection of *Chlamydia pneumoniae* might prevent a person from developing atherosclerosis that might involve platelet aggregation, but Leadlay does not teach any effect directly on platelet aggregation. It is not inherent from Leadlay that there is a biochemical inhibition of platelet aggregation. The withdrawal of this rejection is respectfully requested.

Claims 11-12 stand rejected under 35 U.S.C. §102(e) as being anticipated by Masamune et al. (U.S. 6,025,350). This reference teaches a method of treating a variety of disorders, where the disorders are related to infection by various bacterial and protozoal agents, including *Chlamydia pneumoniae*. This reference does not teach any direct inhibition of platelet aggregation by its subject compounds. Again as with the Leadlay reference, there is no direct effect shown on platelet aggregation. The fact that an antibiotic's successful action against an infection that might lead to a condition involving platelet aggregation would logically prevent such a condition, does not make the direct inhibition of platelet aggregation an inherent property of the antibiotic. Masamune does not show any effect on platelet aggregation such as that discovered by the inventors of the present invention. Prevention of a condition that might result indirectly from a bacterial infection does not make the inhibition of platelet aggregation inherent in this reference. The withdrawal of this rejection is respectfully requested.

Claim Rejections – 35 USC §103

Claims 11-17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Shor et al. (U.S. 5,424,187) in view of Agouridas et al. (U.S. 5,747,467). Shor teaches methods for treating arterial chlamydial granulomatous disease using erythromycins. Agouridas teaches a method of treating *Chlamydia* infections using ketolides. These references, taken singly or in combination, neither teach nor suggest the presently claimed invention, since they do not teach in combination that their compounds have in inhibitory effect on platelet aggregation. A skilled person reading Agouridas might be motivated to try ketolides in the method of Shor, but that does not result in the presently claimed invention. An effect on granulomatous disease by ketolides does not teach that there is an inhibition of platelet aggregation by those compounds. The withdrawal of this rejection is respectfully requested.

It is believed that this response is being filed with a need for a three month extension to the three month shortened period for response, and a petition for a three month extension to July 10, 2006 is included herewith, along with authorization to charge Deposit Account 18-1982 for the required fee. It is believed that no additional fee for claims is due as a result of the present amendment.

The Applicant respectfully requests further examination of this application, and a favorable decision thereon. A prompt Notice of Allowance is respectfully solicited. If the examination of this application can be expedited by a telephone conversation, the Examiner is invited to call the undersigned practitioner, collect if necessary, at 908-231-5922.

Respectfully submitted,

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APPENDIX

PLAVIX®

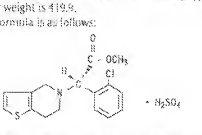
clopidogrel bisulfate tablets

Rx only

DESCRIPTION

PLAVIX (clopidogrel bisulfate) is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Chemically it is methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ and its molecular weight is 419.9.

The structural formula is as follows:



Clopidogrel bisulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether. It has a specific optical rotation of about +56°.

PLAVIX for oral administration is provided as pink, round, biconvex, debossed film-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base.

Each tablet contains hydrogenated castor oil, hydroxypropylcellulose, mannitol, microcrystalline cellulose and polyethylene glycol 6000 as inactive ingredients. The pink film coating contains ferric oxide, hypromellose 2910, lactose monohydrate, titanium dioxide and triacetin. The tablets are polished with Carnauba wax.

CLINICAL PHARMACOLOGY

Mechanism of Action

Clopidogrel is an inhibitor of platelet aggregation. A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with established cardiovascular atherosclerotic disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, unstable angina or the need for vascular bypass or angioplasty. This indicates that platelets participate in the initiation and/or evolution of these events and that inhibiting them can reduce the event rate.

Pharmacodynamic Properties

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation, but an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.

Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of PLAVIX. Repeated doses of 75 mg PLAVIX per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg PLAVIX per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

Pharmacokinetics and Metabolism

After repeated 75-mg oral doses of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit (0.00025 mg/L) beyond 2 hours after dosing. Clopidogrel is extensively metabolized by the liver. The main circulating metabolite is the carboxylic acid derivative, and it too has no effect on platelet aggregation. It represents about 85% of the circulating drug-related compounds in plasma.

Following an oral dose of ^{14}C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration. Covalent binding to platelets accounted for 2% of radiolabel with a half-life of 11 days.

Effect of Food: Administration of PLAVIX (clopidogrel bisulfate) with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolite.

Absorption and Distribution: Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base), with peak plasma levels (≥2 mg/L) of the main circulating metabolite occurring approximately 1 hour after dosing. The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel. Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites.

Clopidogrel and the main circulating metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94%, respectively). The binding is non-saturable *in vitro* up to a concentration of 100 µg/mL.

Metabolism and Elimination: *In vitro* and *in vivo*, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

Special Populations

Geriatric Patients: Plasma concentrations of the main circulating metabolite are significantly higher in elderly (≥75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renally Impaired Patients: After repeated doses of 75 mg PLAVIX per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar to healthy volunteers receiving 75 mg of PLAVIX per day.

Gender: No significant difference was observed in the plasma levels of the main circulating metabolite between males and females. In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Race: Pharmacokinetic differences due to race have not been studied.

CLINICAL STUDIES

The clinical evidence for the efficacy of PLAVIX is derived from two double-blind trials: the CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events), a comparison of Plavix to aspirin, and the CURE study (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), a comparison of Plavix to placebo, both given in combination with aspirin and other standard therapy.

The CAPRIE trial was a 19,185-patient, 304-center, international, randomized, double-blind, parallel-group study comparing PLAVIX (75 mg daily) to aspirin (325 mg daily). The patients randomized had: 1) recent histories of myocardial infarction (within 35 days); 2) recent histories of ischemic stroke (within 6 months) with at least a week of residual neurological signs, or 3) objectively established peripheral arterial disease. Patients received randomized treatment for an average of 1.6 years (maximum of 3 years).

The trial's primary outcome was the time to first occurrence of new ischemic stroke (fatal or not), new myocardial infarction (fatal or not), or

other vascular death. Deaths not easily attributable to nonvascular causes were all classified as vascular.

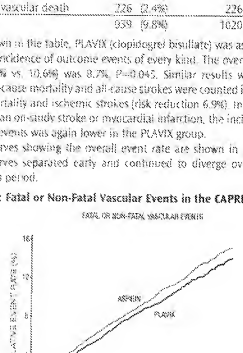
Table 1: Outcome Events in the CAPRIE Primary Analysis

Patients	PLAVIX 9599	Aspirin 9586
IS (fatal or not)	478 (4.6%)	461 (4.8%)
MI (fatal or not)	275 (2.9%)	333 (3.5%)
Other vascular death	226 (2.4%)	226 (2.4%)
Total	939 (9.8%)	1020 (10.6%)

As shown in the table, PLAVIX (clopidogrel bisulfate) was associated with a lower incidence of outcome events of every kind. The overall risk reduction (9.8% vs. 10.6%) was 8.7%, P=0.045. Similar results were obtained when all-cause mortality and all-cause strokes were counted instead of vascular mortality and ischemic strokes (risk reduction 6.9%). In patients who survived an on-study stroke or myocardial infarction, the incidence of subsequent events was again lower in the PLAVIX group.

The curves showing the overall event rate are shown in Figure 1. The event curves separated early and continued to diverge over the 3-year follow-up period.

Figure 1: Fatal or Non-Fatal Vascular Events in the CAPRIE Study



Although the statistical significance favoring PLAVIX over aspirin was marginal (P=0.045), and represents the result of a single trial that has not been replicated, the comparator drug, aspirin, is itself effective (vs. placebo) in reducing cardiovascular events in patients with recent myocardial infarction or stroke. Thus, the difference between PLAVIX and placebo, although not measured directly, is substantial.

The CAPRIE trial included a population that was randomized on the basis of 3 entry criteria. The efficacy of PLAVIX relative to aspirin was heterogeneous across these randomized subgroups (P=0.043). It is not clear whether this difference is real or a chance occurrence. Although the CAPRIE trial was not designed to evaluate the relative benefit of PLAVIX over aspirin in the individual patient subgroups, the benefit appeared to be strongest in patients who were enrolled because of peripheral vascular disease (especially those who also had a history of myocardial infarction) and weaker in stroke patients. In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, PLAVIX was not numerically superior to aspirin.

In the meta-analyses of studies of aspirin vs. placebo in patients similar to those in CAPRIE, aspirin was associated with a reduced incidence of atherothrombotic events. There was a suggestion of heterogeneity in these studies too, with the effect strongest in patients with a history of myocardial infarction, weaker in patients with a history of stroke, and not discernible in patients with a history of peripheral vascular disease. With respect to the inferred comparison of PLAVIX to placebo, there is no indication of heterogeneity.

The CURE study included 12,562 patients with acute coronary syndrome without ST segment elevation (unstable angina or non-Q-wave myocardial infarction) and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischemia. Patients were required to have either ECG changes compatible with new ischemia (without ST segment elevation) or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. The patient population was largely Caucasian (82%) and included 38% women, and 52% patients ≥65 years of age.

Patients were randomized to receive PLAVIX (300 mg loading dose followed by 75 mg/day) or placebo, and were treated for up to one year. Patients also received aspirin (75-325 mg once daily) and other standard therapies such as heparin. The use of GPIIb/IIIa inhibitors was not permitted for three days prior to randomization.

The number of patients experiencing the primary outcome (CV death, MI, or stroke) was 582 (9.30%) in the PLAVIX-treated group and 719 (11.41%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10%-28%; p=0.00009) for the PLAVIX-treated group (see Table 2).

At the end of 12 months, the number of patients experiencing the co-primary outcome (CV death, MI, stroke or refractory ischemia) was 1035 (16.54%) in the PLAVIX-treated group and 1187 (18.83%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6%-21%, p=0.0005) for the PLAVIX-treated group (see Table 2).

In the PLAVIX-treated group, each component of the two primary endpoints (CV death, MI, stroke, refractory ischemia) occurred less frequently than in the placebo-treated group.

Table 2: Outcome Events in the CURE Primary Analysis

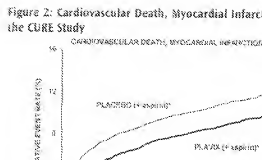
Outcome	PLAVIX (+ aspirin)* (n=6259)	Placebo (+ aspirin)* (n=6303)	Relative Risk Reduction (%) (95% CI)
Primary outcome (Cardiovascular death, MI, Stroke)	582 (9.3%)	719 (11.4%)	20% (10.3, 27.9) P=0.00009
Co-primary outcome (Cardiovascular death, MI, Stroke, Refractory ischemia)	1035 (16.5%)	1187 (18.8%)	14% (6.2, 20.6) P=0.0005¶
All Individual Outcome Events:†			
CV death	318 (5.1%)	349 (5.5%)	7% (-7.7, 20.6)
MI	328 (5.2%)	419 (6.6%)	23% (11.6, 33.4)
Stroke	75 (1.2%)	87 (1.4%)	14% (-17.7, 36.6)
Refractory ischemia	544 (8.7%)	587 (9.3%)	7% (-4.6, 18.0)

* Other standard therapies were used as appropriate.

† The individual components do not represent a breakdown of the primary and co-primary outcomes, but rather the total number of subjects experiencing an event during the course of the study.

The benefits of PLAVIX (clopidogrel bisulfate) were maintained throughout the course of the trial (up to 12 months).

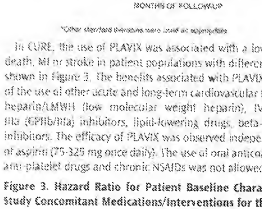
Figure 2: Cardiovascular Death, Myocardial Infarction, and Stroke in the CURE Study



*Other standard therapies were used as appropriate

In CURE, the use of PLAVIX was associated with a lower incidence of CV death, MI or stroke in patient populations with different characteristics, as shown in Figure 3. The benefits associated with PLAVIX were independent of the use of other acute and long-term cardiovascular therapies, including heparin/LMWH (low molecular weight heparin), IV glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, lipid-lowering drugs, beta-blockers, and ACE-inhibitors. The efficacy of PLAVIX was observed independently of the dose of aspirin (75-325 mg once daily). The use of oral anticoagulants, non-study anti-platelet drugs and chronic NSAIDs was not allowed in CURE.

Figure 3. Hazard Ratio for Patient Baseline Characteristics and On-Study Concomitant Medications/Interventions for the CURE Study



*Other standard therapies were used as appropriate

The use of PLAVIX in CURE was associated with a decrease in the use of thrombolytic therapy (71 patients [1.1%] in the PLAVIX group, 126 patients [2.0%] in the placebo group; relative risk reduction of 43%, P=0.0001), and GPIIb/IIIa inhibitors (369 patients [5.9%] in the PLAVIX group, 454 patients [7.2%] in the placebo group, relative risk reduction of 18%, P=0.009). The use of PLAVIX in CURE did not impact the number of patients treated with CABG or PCI (with or without stenting), (2253 patients [36.0%] in the PLAVIX group, 2324 patients [36.9%] in the placebo group; relative risk reduction of 4.0%, P=0.1658).

INDICATIONS AND USAGE

PLAVIX (clopidogrel bisulfate) is indicated for the reduction of atherothrombotic events as follows:

- **Recent MI, Recent Stroke or Established Peripheral Arterial Disease**
  For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, PLAVIX has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.
- **Acute Coronary Syndrome**
  For patients with acute coronary syndrome (unstable angina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG. PLAVIX has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

CONTRAINDICATIONS

The use of PLAVIX is contraindicated in the following conditions:

- Hypersensitivity to the drug substance or any component of the product.
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

WARNINGS

Thrombotic thrombocytopenic purpura (TTP):

TTP has been reported rarely following use of PLAVIX, sometimes after a short exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. (see **ADVERSE REACTIONS**.)

PRECAUTIONS

General

PLAVIX prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, PLAVIX should be discontinued 5 days prior to surgery.

Due to the risk of bleeding and undesirable hematological effects, blood cell count determination and/or other appropriate testing should be promptly considered, whenever such suspected clinical symptoms arise during the course of treatment (see **ADVERSE REACTIONS**).

In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and PLAVIX has not been shown to be more effective than PLAVIX alone, but the combination has been shown to increase major bleeding.

GI Bleeding: In CAPRIE, PLAVIX was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. In CURE, the incidence of major gastrointestinal bleeding was 1.3% vs. 0.7% (PLAVIX + aspirin vs. placebo + aspirin, respectively). PLAVIX should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking PLAVIX.

Use in Hepatically Impaired Patients: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. PLAVIX should be used with caution in this population.

Use in Renally-Impaired Patients: Experience is limited in patients with severe renal impairment. PLAVIX should be used with caution in this population.

Information for Patients

Patients should be told that it may take them longer than usual to stop bleeding, that they may bruise and/or bleed more easily when they take PLAVIX or PLAVIX combined with aspirin, and that they should report any

unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking PLAVIX and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken.

Drug Interactions

Study of specific drug interactions yielded the following results:

Aspirin: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by PLAVIX. PLAVIX potentiated the effect of aspirin on collagen-induced platelet aggregation. PLAVIX and aspirin have been administered together for up to one year.

Heparin: In a study in healthy volunteers, PLAVIX did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by PLAVIX.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of PLAVIX was associated with increased occult gastrointestinal blood loss. NSAIDs and PLAVIX should be coadministered with caution.

Warfarin: Because of the increased risk of bleeding, the concomitant administration of warfarin with PLAVIX should be undertaken with caution (See **PRECAUTIONS–General**.)

Other Concomitant Therapy: No clinically significant pharmacodynamic interactions were observed when PLAVIX was coadministered with **atenolol, nifedipine,** or both atenolol and nifedipine. The pharmacodynamic activity of PLAVIX was also not significantly influenced by the coadministration of **phenobarbital, cimetidine** or **estrogen**.

The pharmacokinetics of **digoxin** or **theophylline** were not modified by the coadministration of PLAVIX (clopidogrel bisulfate).

At high concentrations *in vitro*, clopidogrel inhibits P_{450} (2C9). Accordingly, PLAVIX may interfere with the metabolism of **phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin,** and many **non-steroidal anti-inflammatory agents,** but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with PLAVIX.

In addition to the above specific interaction studies, patients entered into clinical trials with PLAVIX received a variety of concomitant medications including **diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents** (including **insulin**), **antiepileptic agents, hormone replacement therapy, heparins** (unfractionated and LMWH) and **GPIIb/IIIa antagonists** without evidence of clinically significant adverse interactions. The use of oral anticoagulants, non-study anti-platelet drug and chronic NSAIDs was not allowed in CURE and there are no data on their concomitant use with clopidogrel.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg.

Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by oral route in mice).

Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m^2 basis).

Pregnancy

Pregnancy Category B. Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day respectively, 65 and 78 times the recommended daily human dose on a mg/m^2 basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, PLAVIX should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Geriatric Use

Of the total number of subjects in controlled clinical studies, approximately 50% of patients treated with PLAVIX were 65 years of age and over. Approximately 16% of patients treated with PLAVIX were 75 years of age and over.

The observed difference in risk of thrombotic events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Figure 3 (see **CLINICAL STUDIES**). The observed difference in risk of bleeding events with clopidogrel plus aspirin versus placebo plus aspirin by age category is provided in Table 3 (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

PLAVIX has been evaluated for safety in more than 12,500 patients, including over 9,000 patients treated for 1 year or more. The overall tolerability of PLAVIX in CAPRIE was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (7.8%) of patients withdrawing from treatment because of adverse reactions. The clinically important adverse events observed in CAPRIE and CURE are discussed below.

Hemorrhagic: In CAPRIE patients receiving PLAVIX, gastrointestinal hemorrhage occurred at a rate of 2.0%, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for PLAVIX compared to 0.5% for aspirin.

In CURE, PLAVIX use with aspirin was associated with an increase in bleeding compared to placebo with aspirin (see Table 3). There was an excess in major bleeding in patients receiving PLAVIX plus aspirin compared with placebo plus aspirin, primarily gastrointestinal and at puncture sites. The incidence of intracranial hemorrhage (0.1%), and fatal bleeding (0.2%), were the same in both groups.

The overall incidence of bleeding is described in Table 3 for patients receiving both PLAVIX and aspirin in CURE.

Table 3. CURE Incidence of bleeding complications (% patients)

Event	PLAVIX (+ aspirin)* (n=6259)	Placebo (+ aspirin)* (n=6303)	P-value
Major bleeding †	3.7 ‡	2.7 §	0.001
Life-threatening bleeding	2.2	1.8	0.13
Fatal	0.2	0.2	
5 g/dL hemoglobin drop	0.9	0.9	
Requiring surgical intervention	0.7	0.7	
Hemorrhagic strokes	0.1	0.1	
Requiring inotropes	0.5	0.5	
Requiring transfusion (≥4 units)	1.2	1.0	
Other major bleeding	1.6	1.0	0.005
Significantly disabling	0.4	0.3	
Intraocular bleeding with significant loss of vision	0.05	0.03	
Requiring 2-3 units of blood	1.3	0.9	
Minor bleeding ¶	5.1	2.4	<0.001

* Other standard therapies were used as appropriate.

† Life-threatening and other major bleeding.

‡ Major bleeding event rate for PLAVIX + aspirin was dose-dependent on aspirin: <100 mg=2.6%; 100-200 mg= 3.5%; >200 mg=4.9%
Major bleeding event rates for PLAVIX + aspirin by age were: <65 years = 2.9%, ≥65 to <75 years = 4.1%, ≥75 years 5.9%

§ Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100 mg=2.0%; 100-200 mg= 2.3%; >200 mg=4.0%
Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%, ≥65 to <75 years = 3.1%, ≥75 years 3.6%

¶ Led by interruptions of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin/LMWH, and the rate of bleeding in these patients was similar to the overall results.

There was no excess in major bleeds within seven days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (event rate=4.4% PLAVIX + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for PLAVIX + aspirin, and 6.3% for placebo + aspirin.

Neutropenia/agranulocytosis: Ticlopidine, a drug chemically similar to PLAVIX, is associated with a 0.8% rate of severe neutropenia (less than 450 neutrophils/µL). In CAPRIE severe neutropenia was observed in six patients, four on PLAVIX and two on aspirin. Two of the 9599 patients who received PLAVIX and none of the 9586 patients who received aspirin had neutrophil counts of zero. One of the four PLAVIX patients in CAPRIE was receiving cytotoxic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with PLAVIX (clopidogrel bisulfate). In CURE, the numbers of patients with thrombocytopenia (19 PLAVIX + aspirin vs. 24 placebo + aspirin) or neutropenia (3 vs. 3) were similar.

Although the risk of myelotoxicity with PLAVIX (clopidogrel bisulfate) thus appears to be quite low, this possibility should be considered when a patient receiving PLAVIX demonstrates fever or other sign of infection.

Gastrointestinal: Overall, the incidence of gastrointestinal events (e.g. abdominal pain, dyspepsia, gastritis and constipation) in patients receiving PLAVIX (clopidogrel bisulfate) was 27.1%, compared to 29.8% in those receiving aspirin in the CAPRIE trial. In the CURE trial the incidence of these gastrointestinal events for patients receiving PLAVIX + aspirin was 17.7% compared to 12.5% for those receiving placebo + aspirin.

In the CAPRIE trial, the incidence of peptic, gastric or duodenal ulcers was 0.7% for PLAVIX (clopidogrel bisulfate) and 1.2% for aspirin. In the CURE trial the incidence of peptic, gastric or duodenal ulcers was 0.4% for PLAVIX + aspirin and 0.3% for placebo + aspirin.

Cases of diarrhea were reported in the CAPRIE trial in 4.5% of patients in the PLAVIX group compared to 3.4% in the aspirin group. However, these were rarely severe (PLAVIX=0.2% and aspirin=0.1%). In the CURE trial, the incidence of diarrhea for patients receiving PLAVIX + aspirin was 2.1% compared to 2.2% for those receiving placebo + aspirin.

In the CAPRIE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for PLAVIX and 4.0% for aspirin. In the CURE trial, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 0.9% for PLAVIX + aspirin compared with 0.8% for placebo + aspirin.

Rash and Other Skin Disorders: In the CAPRIE trial, the incidence of skin and appendage disorders in patients receiving PLAVIX was 15.8% (0.7% serious); the corresponding rate in aspirin patients was 13.1% (0.5% serious). In the CURE trial the incidence of rash or other skin disorders in patients receiving PLAVIX + aspirin was 4.0% compared to 3.5% for those receiving placebo + aspirin.

In the CAPRIE trial, the overall incidence of patients withdrawing from treatment because of skin and appendage disorders adverse reactions was 1.5% for PLAVIX and 0.8% for aspirin. In the CURE trial, the incidence of patients withdrawing because of skin and appendage disorders adverse reactions was 0.7% for PLAVIX + aspirin compared with 0.3% for placebo + aspirin.

Adverse events occurring in ≥2.5% of patients on PLAVIX in the CAPRIE controlled clinical trial are shown below regardless of relationship to PLAVIX. The median duration of therapy was 20 months, with a maximum of 3 years.

Table 4: Adverse Events Occurring in ≥2.5% of PLAVIX Patients in CAPRIE

Body System Event	% Incidence (% Discontinuation) PLAVIX [n=9599]	Aspirin [n=9586]
Body as a Whole–general disorders		
Chest Pain	8.3 (0.2)	8.2 (0.3)
Accidental/Inflicted Injury	7.9 (0.1)	7.3 (0.1)
Influenza-like symptoms	7.5 (<0.1)	7.0 (<0.1)
Pain	6.4 (0.1)	6.3 (0.1)
Fatigue	3.5 (0.1)	3.4 (0.1)
Cardiovascular disorders, general		
Edema	4.1 (<0.1)	4.5 (<0.1)
Hypertension	4.3 (<0.1)	5.1 (<0.1)
Central & peripheral nervous system disorders		
Headache	7.6 (0.3)	7.2 (0.2)
Dizziness	6.2 (0.2)	6.7 (0.3)
Gastrointestinal system disorders		
Abdominal pain	5.6 (0.7)	7.1 (1.0)
Dyspepsia	5.2 (0.6)	6.1 (0.7)
Diarrhea	4.5 (0.4)	3.4 (0.5)
Nausea	3.4 (0.5)	3.6 (0.4)
Metabolic & nutritional disorders		
Hypercholesterolemia	4.0 (0)	4.4 (<0.1)
Musculo-skeletal system disorders		
Arthralgia	6.3 (0.1)	6.2 (0.1)
Back Pain	5.8 (0.1)	5.3 (<0.1)
Platelet, bleeding, & clotting disorders		
Purpura/Bruise	3.3 (0.3)	3.7 (0.1)
Epistaxis	2.9 (0.2)	2.5 (0.1)
Psychiatric disorders		
Depression	3.6 (0.1)	3.9 (0.2)
Respiratory system disorders		
Upper resp tract infection	8.7 (<0.1)	8.3 (<0.1)
Dyspnea	4.5 (0.1)	4.7 (0.1)
Rhinitis	4.2 (0.1)	4.2 (<0.1)
Bronchitis	3.7 (0.1)	3.7 (0)
Coughing	3.1 (<0.1)	2.7 (<0.1)
Skin & appendage disorders		
Rash	4.2 (0.5)	3.5 (0.2)
Pruritus	3.3 (0.3)	1.6 (0.1)
Urinary system disorders		
Urinary tract infection	3.1 (0)	3.5 (0.1)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Adverse events occurring in ≥2.5% of patients on PLAVIX in the CURE controlled clinical trial are shown below regardless of relationship to PLAVIX.

Table 5: Adverse Events Occurring in ≥2.0% of PLAVIX Patients in CURE

Body System Event	% Incidence (% Discontinuation) PLAVIX (+ aspirin)* [n=6259]	Placebo (+ aspirin)* [n=6303]
Body as a Whole–general disorders		
Chest Pain	2.7 (<0.1)	2.8 (0.0)
Central & peripheral nervous system disorders		
Headache	3.1 (0.1)	3.2 (0.1)
Dizziness	2.8 (0.3)	2.0 (<0.1)
Gastrointestinal system disorders		
Abdominal pain	2.3 (0.3)	2.0 (0.5)
Dyspepsia	2.0 (0.1)	1.9 (<0.1)
Diarrhea	2.1 (0.1)	2.2 (0.1)

*Other standard therapies were used as appropriate.

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving PLAVIX (clopidogrel bisulfate) in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to PLAVIX, in general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE).

Autonomic Nervous System Disorders: Syncope, Palpitation. *Body as a Whole–general disorders:* Asthenia, Fever, Hernia. *Cardiovascular disorders:* Cardiac failure. *Central and peripheral nervous system disorders:* Cramps legs, Hypoaesthesia, Neuralgia, Paraesthesia, Vertigo. *Gastrointestinal system disorders:* Constipation, Vomiting. *Heart rate and rhythm disorders:* Fibrillation atrial. *Liver and biliary system disorders:* Hepatic enzymes increased. *Metabolic and nutritional disorders:* Gout, hypernatremia, non-protein nitrogen (NPN) increased. *Musculo-skeletal system disorders:* Arthritis, Arthrosis. *Platelet, bleeding & clotting disorders:* GI hemorrhage, hematoma, platelets decreased. *Psychiatric disorders:* Anxiety, Insomnia. *Red blood cell disorders,* Anemia. *Respiratory system disorders,* Pneumonia, Sinusitis. *Skin and appendage disorders:* Eczema, Skin ulceration. *Urinary system disorders:* Cystitis. *Vision disorders:* Cataract, Conjunctivitis.

Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received PLAVIX in the CAPRIE or CURE controlled clinical trials are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in CURE).

Body as a whole: Allergic reaction, necrosis ischemic. *Cardiovascular disorders:* Edema generalized. *Gastrointestinal system disorders:* Gastric ulcer perforated, gastritis hemorrhagic, upper GI ulcer hemorrhagic. *Liver and Biliary system disorders:* Bilirubinemia, hepatitis infectious, liver fatty. *Platelet, bleeding and clotting disorders:* hemarthrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia. *Red blood cell disorders,* Anemia aplastic, anemia hypochromic. *Reproductive disorders, female,* Menorrhagia. *Respiratory system disorders:* Hemothorax. *Skin and appendage disorders,* Bullous eruption, rash erythematous, rash maculopapular, urticaria. *Urinary system disorders:* Abnormal renal function, acute renal failure. *White cell and reticuloendothelial system disorders:* Agranulocytosis, granulocytopenia, leukemia, leukopenia, neutrophils decreased.

Postmarketing Experience
The following events have been reported spontaneously from worldwide postmarketing experience.

- *Body as a whole*
  - hypersensitivity reactions, anaphylactoid reactions, serum sickness
- *Central and Peripheral Nervous System disorders*
  - confusion, hallucinations, taste disorders
- *Hepato-biliary disorders*
  - abnormal liver function test, hepatitis (non-infectious), acute liver failure
- *Platelet, Bleeding and Clotting disorders*
  - cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal hemorrhage)
  - thrombotic thrombocytopenic purpura (TTP) – some cases with fatal outcome – (see **WARNINGS**)
  - agranulocytosis, aplastic anemia/pancytopenia
  - conjunctival, ocular and retinal bleeding
- *Respiratory, thoracic and mediastinal disorders*
  - bronchospasm, interstitial pneumonitis
- *Skin and subcutaneous tissue disorders*
  - angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus
- *Renal and urinary disorders*
  - glomerulopathy, increased creatinine levels
- *Vascular disorders*
  - vasculitis, hypotension
- *Gastrointestinal disorders*
  - colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis
- *Musculoskeletal, connective tissue and bone disorders*
  - myalgia

OVERDOSAGE
Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.

Recommendations About Specific Treatment:
Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of PLAVIX if quick reversal is required.

DOSAGE AND ADMINISTRATION
Recent MI, Recent Stroke, or Established Peripheral Arterial Disease
The recommended daily dose of PLAVIX is 75 mg once daily.

Acute Coronary Syndrome
For patients with acute coronary syndrome (unstable angina/non-Q-wave MI), PLAVIX should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with PLAVIX. In CURE, most patients with Acute Coronary Syndrome also received heparin acutely (see **CLINICAL STUDIES**).

PLAVIX can be administered with or without food.

No dosage adjustment is necessary for elderly patients or patients with renal disease. (See **Clinical Pharmacology: Special Populations**.)

HOW SUPPLIED
PLAVIX (clopidogrel bisulfate) is available as a pink, round, biconvex, film-coated tablet debossed with "75" on one side and "1171" on the other. Tablets are provided as follows:

NDC 63653-1171-6 bottles of 30
NDC 63653-1171-1 bottles of 90
NDC 63653-1171-5 bottles of 500
NDC 63653-1171-3 blisters of 100

Storage
Store at 25° C (77° F); excursions permitted to 15°–30° C (59°–86° F) [See USP Controlled Room Temperature].

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